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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,943	SAMPATH ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3, 5-15, 17--29, 76, and 123-125* is/are pending in the application.

4a) Of the above claim(s) *5,7,29 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,8-15,17-28 and 123-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner for this Application is now Daniel C. Gamett.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/16/2005 has been entered.

2. The Examiner notes the following inconsistencies in Applicant's submission filed on 05/16/2005. On p. 7, the Remarks state that, "After entry of this Amendment, claims 1, 3, 8-28, and 123-125 will be pending." However the actual listing of the claims indicates that claims 5, 7, 29, and 76 are withdrawn, and therefore still pending. Claims 5, 7, 29, and 76 are withdrawn from consideration pursuant to the requirement for Restriction/Election of 09/09/2002. Furthermore, the claim listing of 05/16/2005 indicates that claim 16 is cancelled. This appears to be the Applicant's intent, as the limitations of original claim 16 have been incorporated into claims 1 and 3. Finally, the claim listing of 05/16/2005 seems to indicate that Applicant intends for claim 6 to remain under consideration. Therefore, claims 1, 3, 6, 8-15, 17-28, and 123-125 are under consideration insofar as they read upon elected species 'renal tissue' in this office action.

Claim Rejections Withdrawn

3. The rejection of claims 1, 6, 12-15, 20, and 23-28 under 35 U.S.C. 103(a) as unpatentable over WO 93/04692 in view of U.S. Patent No. 6,096,706 is withdrawn in view of Applicant's

amendment and argument that WO 93/04692 does not teach administering a morphogen at least 6 hours after creating a local defect site.

New Objections/Rejections

Specification

4. The disclosure is objected to because of the following informalities: In figure 1, the relationship between the bar graph data and the experimental groups described on p.46, lines 10-21 is not clear. The description of figure 1 (p.9, line 6) merely states, "Figure 1A-1C is a graph showing bone forming activity induced by systemic OP-1." What do the clear and shaded bars represent? A similar lack of clarity exists for figures 2 and 3. Furthermore, the relationship between figure 2 and any experimental example is not indicated. In figure 3, the relationship of the y axis labels to the experimental groups described in Example 7, pp. 47-48, is not clear.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3, 6, 8-15, 17-28, and 123-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1,3 (from which all other claims depend), and 125 each recite method step "(a) creating a local defect site in a mammal accessible to progenitor cells". While the specification indicates that the defect site should be accessible to progenitor cells, the claim could mean that it is the mammal that is accessible to progenitor cells.

8. Claims 1,3, and 125 are additionally unclear regarding step (b) administering at least 6 hours after creating the local defect site, said candidate morphogenic protein..." A "permissive" site is defined on p.5, lines 18-21 as follows, "As contemplated herein, a "permissive" site is a local site of a tissue defect in need of repair and to which progenitor cells are accessible. Mesenchymal progenitor cells typically become available to a defect locus at least by 6-24 hours post trauma as part of the inflammatory response triggered by the initial trauma." This seems to indicate that 6 hours post trauma is required to *create* a defect site accessible to progenitor cells, which means that performance of step (a) necessarily includes a 6-hour waiting period. In that case, step (b) would add on another 6 hours before the candidate morphogen is administered. Yet the specification shows 6 hour post trauma administrations in Examples 3,7, 9, and 11. Thus, step (b) is unclear.

9. Claims 15 and 123 are additionally unclear as they specify that the candidate morphogen is administered *at a time* when mesenchymal progenitor cells are accessible, and that the local defect site is *permissive*. These claims create doubt in the mind of the skilled artisan as to whether claims 1 or 3 were properly understood. Before reading claim 15 or 123, a skilled artisan would expect that performing step (a) would preclude choosing a time when progenitor cells were not available or the site was not permissive.

10. Claims 1,3, and 125 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited (steps a and b in the instant case), a detection step in which the reaction steps are quantified or visualized (steps c and d), and a correlation step describing how the results of the assay allow for the determination.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 3, 6, 8-15, 17-28, and 123-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the

art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claims purport to describe general methods to evaluate the morphogenic or tissue regenerating activity of candidate proteins. The methods require, first, the creation of a specific kind of defect, followed by systemic administration of a candidate protein and evaluation of new tissue formation and/or replacement tissue regeneration.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification does not include any example that is directly relevant to the elected species of renal tissue. The specification is unclear

about how to carry out the claimed method, specifically regarding steps "(a) creating a local defect site in a mammal accessible to progenitor cells" and (b) administering at least 6 hours after creating the local defect site, said candidate morphogenic protein..." Regarding these steps, p.5, lines 18-21 states, "As contemplated herein, a "permissive" site is a local site of a tissue defect in need of repair and to which progenitor cells are accessible. Mesenchymal progenitor cells typically become available to a defect locus at least by 6-24 hours post trauma as part of the inflammatory response triggered by the initial trauma." The term "typically" suggests that progenitor cells may become available sooner than 6 hours post trauma in certain circumstances. Many tissues have resident mesenchymal progenitor cells, so it would be expected that some cells would be accessible immediately after trauma. Applicant seems to be suggesting that a certain threshold number of progenitor cells near the site of damage must be achieved, but does not provide the skilled artisan with a way of knowing that enough cells are present except to suggest that waiting at least 6 hours would be a good idea. 6-hour time points of administration are given in Examples 3,7, 9, and 11, but in no case was it established that 6 hours was either necessary or sufficient as a general rule. It is not clear when the when the 6 hours should even begin in cases where the insult does not cause instantaneous damage, as with administration of a toxin. In the model of oral mucositis in example 13, morphogen administration began 3 days *before* the beginning of the mucositis-induction procedure. Many of the Examples (1-7) were not relevant to the methods as claimed because the endpoint was ectopic bone formation and not regeneration of a site of damage. In theses examples, simply damaging a tissue and waiting 6 hours is not sufficient to make some tissues "accessible to progenitor cells", a collagen implant is required, and even then the results varied with the type of

collagen and the location of the site (see p. 43, lines 5-8 and p. 46, lines 19-21). Example 8 includes the prediction that "is anticipated that systemically administered morphogenic protein will induce osteogenesis sufficient to repair the ulna defect" (p.49, lines 12-14), apparently even in animals that did not receive a collage implant (this is not clear), but this merely prophetic and no data are shown. Example 9 (p. 49, line 15- p.50, line 15) describes a model of pulmonary fibrosis in which there is no stated requirement for a collagen implant. In this model, the measured outcome is reduction in fibrotic lesions and not "new tissue formation" or "replacement tissue regeneration" as in the instant claims and only "anticipated" results are presented. Examples 10-16 describe models of damage to the myocardium, liver, oral mucosa, duodenum, retina, and medial femoral condyle, each with a different means of inducing damage, different timing and dosing protocol for administration of morphogen, and different criteria for evaluating results. Significantly, only "expected" results are given and there is no guidance as to how to perform step (a) of the claimed methods. Thus, the instant specification does not provide certain guidance as to what will or will not work even in the given examples and it does not establish a basis for predicting what will work for tissues not exemplified. Apparently, the only way of knowing that a local defect site is or was "accessible to progenitor cells" is by completing the method and obtaining a positive result. The lack of actual results is significant because, if the claimed method is to be performed with candidate morphogens with unknown activity, the only way to interpret a negative result will be by comparison to a positive control.

The state of the prior art and the predictability or lack thereof in the art: As evidenced the rejections under 35 U.S.C. 102 and 103 of record, the art teaches that it is possible to systemically administer OP-1 and achieve repair of a local site of damage. *A priori*, the skilled

artisan would expect that the effect of systemic administration of a morphogenic protein on tissue repair would vary with the type of tissue, the type of damage, and the stability of the morphogenic protein. The art does not recognize a uniform requirement of at least 6 hours for infiltration of significant numbers of progenitor cells into a site of damage. Thus the instant disclosure and the prior art together do not teach the methods as claimed. A skilled artisan performing research in this field might find, after considerable research and after the results had been analyzed, that he/she had performed a method similar to that of claims 1,3, or 125. In such a case, the skilled artisan cannot be said to have been taught by the prior art nor by the instant specification.

The breadth of the claims and the quantity of experimentation needed: The claims read upon a method in which an experimental lesion may be created in any of several different tissues and *if the tissue is permissive*, systemic administration of a candidate morphogenic protein will result in new tissue formation or replacement tissue regeneration. The skilled artisan would first need to determine a positive control morphogenic protein for each tissue. In some cases, this would entail confirmation of the speculative suggestions provided by the instant specification and in others (e.g. thyroid) it would require a completely new discovery. The skilled artisan would need to perform undue experimentation to determine if a given tissue is permissive, as the only test for permissiveness is to complete the assay.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DCG
Art Unit 1647
6 July 2005

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